REMARKS

Claims 1 and 3-17 are pending. Claim 1 has been amended to clarify that the permeation enhancing agent acts to enhance the transmucosal delivery of a pharmaceutically active compound to a subject. Support for the amendment can be found at, for example, paragraphs **[0002]** and **[0020]** of the specification. No new matter has been added. Claims 1 and 3-17 are presented for examination. Claims 1 and 3-17 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Hellstrand et al. (U.S. Patent No. 6,071,942). Reconsideration and withdrawal of the present rejections in view of the amendment to Claim 1 and comments presented herein are respectfully requested.

Claims 1 and 3-17 are non-obvious in view of Hellstrand et al. (U.S. Patent No. 6,071,942)

Claims 1 and 3-17 were rejected under 35 U.S.C. §103(a) as being unpatentable over Hellstrand et al. (U.S. Patent No. 6,071,942) (the '942 patent). The claims of the present invention are directed to a transmucosally administrable composition comprising a pharmaceutically active compound and a permeation enhancer such as histamine, histamine phosphate, or histamine dihydrochloride, wherein the permeation enhancing agent acts to facilitate the delivery of a pharmaceutical compound transmucosally. The '942 patent is drawn to methods of achieving stable, elevated levels of blood histamine comprising injection of histamine or histamine-like compounds. According to the Examiner, it would have been obvious to one of ordinary skill in the art to follow the teachings of the '942 patent in order to improve the effectiveness of pharmaceutically active agents in the blood stream. Applicant respectfully disagrees.

In establishing a *prima facie* case for obviousness, three criteria must each be met. First, there must be some suggestion or motivation to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference or a combination of references must teach or suggest all of the limitations of the claims. M.P.E.P. §2143. Applicant submits that the Examiner has failed to establish a *prima facie* case for obviousness and thus, requests that the rejection of Claims 1 and 3-17 under 35 U.S.C. §103(a) be withdrawn.

There is no motivation to modify the '942 patent to arrive at the claimed invention

Obviousness can only be established by modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so

found either in the reference itself or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988). The Examiner has pointed to no motivation to modify the '942 to arrive at the claimed compositions. The '942 patent is directed to methods for achieving a stable, elevated blood histamine level by injecting discrete amounts of histamine over a period of time between one and thirty minutes to achieve an elevated blood histamine level of at least 0.2 μM/L. The elevated levels of blood histamine are achieved via persistent administration of histamine over a well-defined time period. As the specification of the '942 patent makes clear, it was previously believed that histamine had an extremely short half-life on the order of seconds in circulation. The invention described in the '942 patent is based, in part, on the discovery that sustained levels of histamine in the blood above 0.2 μM/L could be achieved using delivery times much longer than typical injection and much shorter than typical infusion. By increasing blood histamine levels, it was believed that natural killer (NK) cell cytotoxicity could be enhanced.

A review of the '942 patent reveals that the inventors neither considered nor appreciated the role of histamine as a permeation enhancing agent, as is presently claimed. Instead, the thrust of the '942 patent is directed at achieving stable, elevated blood histamine levels in order to stimulate NK cell activity and cytotoxic T-lymphocyte (CTL) cytotoxicity through the suppression of an inhibitory signal generated by monocytes. See Col.3, lines 55-67 of the '942 patent. The inhibitory effects of monocytes on cytotoxic effector cells such as NK cells and CTLs were believed to result from the generation of hydrogen peroxide by monocytes. By injecting histamine such that a stable, elevated level of blood histamine was achieved, histamine would reduce the level of hydrogen peroxide produced by monocytes, thereby removing the inhibitory effects of monocytes and augmenting the activity of NK cells and CTLs. Thus, in the context of the '942 patent, histamine acted as the pharmaceutically effective agent for treating, *inter alia*, malignancies or viral infections through the promotion of NK cell and CTL activation rather than as a permeation enhancing agent. Notably, the '942 patent is silent with respect to any permeation enhancing properties of histamine.

Absent an appreciation of the role of histamine as a permeation enhancing agent, a skilled artisan would not have been motivated to modify the teachings of the '942 patent to arrive at the claimed invention. In contrast to the teachings of the '942 patent, the present application is based on the heretofore unknown property of histamine to enhance the delivery of a pharmaceutically

active components through the mucosal membranes and into the bloodstream. Histamine, an inflammatory mediator, enhances tissue uptake of a pharmaceutically effective agent such as a chemotherapeutic. Its effect on fine vessels is to cause edema by increasing the flow of lymph and lymph proteins into the extracellular space and also by promoting the formation of gaps between endothelial cells, thus increasing transcapillary vesicular transport. The present invention is based in part on the discovery that histamine can enhance the permeation of a pharmaceutically active compound across a transmucosal membrane and across mucosal membranes. The same mechanism by which histamine and histamine-like compounds cause edema in fine vessels can be harnessed to increase drug concentrations in, for example, tumor tissues. The beneficial role of histamine in the present invention therefore relates to its ability to facilitate the transport of a pharmaceutically active agent such as a chemotherapeutic into the bloodstream.

The mere fact that the teachings of '942 patent might be modified does not render the resultant modification obvious unless the prior art also suggests the desirability of the modification. See In re Mills, 16 U.S.P.Q.2d 1430 (Fed Cir. 1990); See, also M.P.E.P. §2143.01. The '942 patent is silent with respect to the advantages of a transmucosally administrable composition comprising a permeation enhancing agent such as histamine in combination with another pharmaceutically active compound. As discussed above, the '942 patent relates primarily to the achievement of stable, elevated levels of histamine in the blood by injecting histamine over a finite period of time. By contrast, the claims of the present invention are directed to transmuscosally administrable compositions comprising a pharmaceutically active compound and a permeation enhancing agent such as histamine. Transmucosal administration of a pharmaceutically active compound facilitated by histamine is quite different from administration of histamine as the active ingredient via injection. As detailed in the specification of the present invention, transmucosal administration of drugs offers advantages over other routes of administration, such as rapid onset of action, achievement of high levels of active ingredient into the blood, elimination of the need for a hypodermic needle, and circumvention of first pass effect of hepatic metabolism. See paragraphs **[0015]** and **[0016]** of the specification. The desirability of utilizing histamine or histamine-like compounds as permeation enhancing agents for transmucosal administration of a different active compound was neither recognized

nor suggested by the '942 patent. Accordingly, Claims 1 and 3-17 are not obvious in view of the '942 patent.

There is no reasonable expectation of success in achieving the claimed invention by modifying the '942 patent

The Federal Circuit has held that prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091 (Fed. Cir. 1986). Because the '942 reference fails to disclose any information that would lead a skilled artisan to believe that histamine would affect the permeability of the dermis, the peritoneal membrane, or any other structure in the body, Applicant submits that a skilled artisan would have no reasonable expectation of success in achieving the claimed invention in view of the teachings of the '942 patent. The '942 patent neglects to provide any information to suggest the desirability of histamine in any formulation for enhancing transdermal or transmembrane delivery of pharmaceutically active compounds. Thus, there is no reasonable expectation of a successful increase in dermal or membrane permeability with histamine as is presently claimed based upon the teachings of the '942 patent. In contrast to the presently claimed invention, the cited reference fails to disclose any effect that histamine might have on dermal or membrane permeability. Moreover, it fails to provide a reasonable expectation of successfully using histamine as an agent to enhance the transdermal or transmembrane delivery of a pharmaceutically active compound. Accordingly, the rejection of the claims under 35 U.S.C. §103(a) in view of the '942 patent should be withdrawn.

The '942 patent fails to teach each and every limitation of the claims

In order to establish a case for obviousness, the Examiner must cite prior art that teaches or suggests all the claim limitations. See M.P.E.P. § 2143.03. Applicant submits that the pending claims are non-obvious in view of the '942 patent because the '942 patent neither teaches nor suggests the role of histamine as a permeation enhancing agent. Moreover, in addition to failing to recognize the role of histamine as permeation enhancing agent, the prior art neglects to teach the claimed ranges for histamine concentrations in the compositions.

The Examiner contends that the pending claims are obvious because the stated ranges for histamine concentrations in the compositions of the invention can be determined through routine experimentation. The Examiner also asserts that the claimed ranges and concentrations lack criticality and are therefore obvious in light of the prior art. The Examiner asserts that a skilled

artisan would have been motivated, based upon the teachings of the '942 patent, to create transmucosal delivery formulations wherein the formulation delivers its active agents more efficiently to the bloodstream. Applicant respectfully disagrees.

As detailed in Applicant' previous response to the Final Office Action, Applicant reminds the Examiner that it is well-established that before optimum ranges or values of a particular variable are characterized as a result of routine experimentation, the variable must first be recognized as a result-effective variable, *i.e.,* a variable which achieves a recognized result. *See* M.P.E.P §2144.05(II)(B) citing *In re Antonie*, 559 F.2d 618, 195 U.S.P.Q. 6 (C.C.P.A. 1977). In *In re Antonie*, the applicant had discovered an optimum ratio of tank volume to contactor area (0.12 gal./sq ft) which maximized treatment capacity of a wastewater treatment device. While the prior art disclosed tank volume and contactor area, the C.C.P.A. allowed the claims because the prior art did not recognize that treatment capacity is a function of the tank volume to contractor ratio. In other words, the optimized ratio was not recognized in the art to be a result-effective variable.

The cited prior art reference contain no suggestion that histamine could be used as a permeation enhancing agent and therefore does not recognize the permeation enhancement properties of histamine as a result-effective variable to be optimized. The use of a permeation enhancing agent wherein the agent is selected from the group consisting of histamine and histamine agonists is a limitation of the pending claims that is not taught or suggested by the cited reference. With no disclosure or suggestion that histamine could serve as a permeation enhancer in the '942 reference, a skilled artisan would not be motivated by the reference to optimize the transmucosal dose of histamine needed to produce the optimal level of permeation enhancement by histamine. Therefore, Applicant asserts that the claims are non-obvious in view of the '942 patent.

Conclusion

The Examiner has maintained his rejection of the claims under 35 U.S.C. §103 in light of one prior art reference. However, the '942 patent neither discloses nor suggests the permeation enhancing properties of histamine. There are no teachings in the reference that would lead one with skill in the art to have a reasonable expectation of successful permeation enhancement with the use of histamine. Without any evidence that histamine can enhance the permeation of or the entry into the dermal or mucosal layers by other pharmaceutically active agents, the '942 patent

fails to teach or suggest the limitations of the present claims. Moreover, the disclosure in the '942 patent cannot provide a basis for finding the optimal dosage of histamine as a permeation enhancer. For these reasons, Applicant respectfully requests withdrawal of the rejection of the claims under 35 U.S.C. §103 and allowance of the application.

Applicant has endeavored to address all issues raised in the Office Action. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: 12/01/04

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